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RNA interference as a therapeutic tool against viral infections.

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Introduction

RNA interference (RNAi) is a naturally occurring cellular mechanism that regulates gene expression by silencing specific messenger RNA (mRNA) molecules. Since its discovery, RNAi has emerged as a powerful therapeutic strategy, particularly in the fight against viral infections. By targeting viral genomes or host factors essential for viral replication, RNAi offers a precise, adaptable, and potentially broad-spectrum antiviral approach. Chemical modifications of siRNAs, such as 2'-O-methylation, have been employed to reduce immunogenicity and enhance stability. Clinical trials have generally reported favorable safety profiles, but long-term effects require further investigation. Several RNAi-based therapeutics have reached clinical trials for viral infections. Notably, JNJ-3989 for HBV and ALN-RSV01 for RSV have demonstrated efficacy and safety in early-phase studies. The success of RNAi drugs in other fields—such as patisiran for hereditary transthyretin amyloidosis—has paved the way for antiviral applications. Regulatory agencies are increasingly receptive to RNAi therapies, recognizing their precision and adaptability. Continued investment in clinical development and manufacturing infrastructure will accelerate their availability. As traditional antiviral therapies face challenges such as drug resistance and limited efficacy against emerging viruses, RNAi presents a promising frontier in molecular medicine [1].

RNAi is mediated by small RNA molecules—primarily small interfering RNAs (siRNAs) and microRNAs (miRNAs). These molecules guide the RNA-induced silencing complex (RISC) to complementary mRNA sequences, leading to their degradation or translational repression. In therapeutic applications, synthetic siRNAs are designed to target viral RNA sequences, thereby halting replication and reducing viral load. The specificity of RNAi allows for selective targeting of viral genes without affecting host cellular functions, minimizing off-target effects and toxicity. Moreover, RNAi can be engineered to target conserved regions of viral genomes, making it effective against multiple strains or variants [2].

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are major global health concerns. RNAi-based therapies have shown promise in silencing HBV surface antigen (HBsAg) and other viral transcripts. For example, the investigational drug JNJ-3989 (formerly ARO-HBV) uses siRNAs to reduce HBV RNA and protein levels, leading to sustained viral suppression. In HCV, RNAi has been used to target the internal ribosome entry site (IRES) and nonstructural proteins essential for replication. Although direct-acting antivirals (DAAs) have revolutionized HCV treatment, RNAi remains a valuable tool for resistant or complex cases [3].

HIV presents unique challenges due to its integration into the host genome and high mutation rate. RNAi strategies have focused on silencing viral genes such as gag, pol, and env, as well as host factors like CCR5 and CD4 that facilitate viral entry. Studies have demonstrated that siRNAs targeting CCR5 can block HIV infection in vitro and in animal models. Gene therapy approaches using lentiviral vectors to deliver RNAi constructs into hematopoietic stem cells are being explored to create HIV-resistant immune cells. While clinical translation is ongoing, RNAi offers a potential pathway to functional cure or long-term viral suppression. Respiratory viruses such as influenza, respiratory syncytial virus (RSV), and SARS-CoV-2 have been targeted using RNAi. siRNAs directed against influenza polymerase genes have shown efficacy in reducing viral replication and improving survival in animal models [4].

During the COVID-19 pandemic, RNAi was investigated as a rapid-response therapeutic. siRNAs targeting conserved regions of the SARS-CoV-2 genome, including the spike and nucleocapsid proteins, demonstrated antiviral activity in vitro. Although mRNA vaccines dominated the therapeutic landscape, RNAi remains a viable option for future respiratory outbreaks. Effective delivery of RNAi molecules to target tissues remains a major hurdle. Naked siRNAs are unstable in circulation and poorly penetrate cells. To overcome this, various delivery systems have been developed: Used in mRNA vaccines, LNPs protect siRNAs and facilitate cellular uptake. Adeno-associated viruses (AAVs) and lentiviruses can deliver RNAi constructs with high efficiency. These systems enhance stability and target specificity. Targeted delivery to infected tissues, such as the liver or lungs, is critical for therapeutic success and minimizing off-target effects. While RNAi is highly specific, unintended silencing of non-target genes can occur due to partial sequence homology. Computational design and rigorous screening are essential to minimize off-target effects. Immune activation is another concern, as siRNAs can trigger innate immune responses via Toll-like receptors (TLRs) [5].

Conclusion

RNA interference represents a transformative approach to antiviral therapy, offering precision, adaptability, and broad-spectrum potential. From hepatitis and HIV to respiratory viruses, RNAi has demonstrated efficacy in silencing viral genes and modulating host responses. While challenges remain in delivery and safety, ongoing research and clinical development continue to unlock its promise. As the world faces evolving viral threats, RNAi stands as a powerful tool in the arsenal of molecular medicine.

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